Systemic arteriovenous malformations: a feature of advanced liver disease

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Abstract

Arterial and arteriovenous abnormalities are reported in association with advanced liver disease, those most commonly recognised are spider naevi, pulmonary arteriovenous shunts, and generalised vasodilatation. The first two cases of peripheral systemic arteriovenous malformations in association with cirrhosis are reported. After liver transplantation in one of these patients the vascular malformation regressed. A review of published works shows that other vascular complications of advanced liver disease such as pulmonary shunts and generalised vasodilatation also regress after orthotopic liver transplantation.

(Gut 1994; 35: 1145-1147)

Vascular anomalies and cardiovascular disturbance are recognised complications of chronic liver disease. Those most commonly seen include spider naevi, pulmonary arteriovenous abnormalities,¹ and a low systemic vascular resistance high cardiac output state.²

We report a new association between vascular anomalies and liver disease in two cases with arteriovenous malformations in the peripheral systemic circulation. One of the

patients with a digital arteriovenous malformation went on to require liver transplantation, after which the vascular abnormality regressed. We discuss the associations between advanced liver disease and cardiovascular anomalies, the impact of liver transplantation on vascular disturbances and its implications for the aetiology of these lesions.

Case report 1

A 59 year old woman presented in 1989 with abdominal swelling and deep jaundice after a five year history of alcohol abuse (>100 units/week). On examination she had palmar erythema, multiple spider naevi, jaundice, hepatosplenomegaly, and tense ascites. Her initial investigations showed an international normalised ratio (INR) of 1.5, albumin 25, and alanine aminotransferase (ALT) 205. Autoimmune profile and viral hepatitis markers were negative and a liver biopsy showed alcoholic cirrhosis with an active hepatitis. One year later she presented again with decompensated liver failure secondary to a urinary tract infection and continued high alcohol intake, INR 2.1, albumin 21, ALT 342, when a pulsatile lesion, on the tip of the left index finger, was noted (Fig 1). The patient confirmed that the lesion had been enlarging over a few months and on two occasions had bled profusely. Digital subtraction angiography showed a vascular blush during bolus injection consistent with an arteriovenous malformation. Since the abnormality was first noted it has continued to enlarge in association with further deterioration of liver function because of continued alcohol abuse.

Case report 2

A 53 year old white woman presented in 1987 with jaundice, pruritus, and abdominal swelling. Her past medical history was unremarkable. On examination at first presentation she was icteric, had multiple spider naevi, periorbital xanthelasmata, hepatosplenomegaly, and ascites. Initial investigations suggested a biliary cirrhosis with an alkaline phosphatase (ALP) of 753, bilirubin 76, ALT 34, and albumin 32. Routine haematology tests were all normal except an INR of 1.5. Autoimmune profile showed positive anti-mitochondrial antibodies at 1:640 and liver biopsy confirmed histological changes consistent with primary biliary cirrhosis. She was followed up uneventfully for three years and then presented with bleeding from oesophageal varices, which were treated with a course of

Figure 1: Pulsatile lesion at tip of left index finger of patient 1.

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Figure 2: Large pulsatile lesion (maximum 2.5 cm diameter) in right index finger of patient 2.

injection sclerotherapy. At this time a pulsatile lesion on the right index finger was noted (Fig 2), which the patient informed us had bled profusely intermittently over the preceding three years. Digital subtraction angiography of the lesion showed a central feeding artery and early venous filling, during the arterial phase of rapid bolus injection, consistent with an arteriovenous malformation (Fig 3). A year later (1991) she had a series of important variceal bleeds, which were controlled with intravenous octreotide and sclerotherapy. During this time her liver function had continued to deteriorate (INR 1.8, ALP 986, albumin 28) and the arteriovenous malformation increased in size considerably. Later that year she had an orthotopic liver transplantation. This was complicated by a pulmonary embolus but otherwise she made an uneventful recovery, maintained with prednisolone and FK506. Three weeks after her transplant surgery the lesion on the index finger had halved in size and her liver function had returned to normal. By nine months after the transplant the lesion had significantly regressed but is still visible.

Discussion

This is the first report of systemic vascular arteriovenous malformations in advanced liver disease, although a number of vascular and circulatory abnormalities have been recognised in association with cirrhosis for many years.

Spider naevi, the commonest vascular abnormalities seen in liver disease, are formed by a dilated superficial arteriole surrounded by fine radiating branches. They can occur in a few other situations such as during pregnancy

or during treatment with oestrogen containing drugs, but their presence in significant numbers is highly suggestive of chronic liver disease with significant dysfunction. Moreover, a crop of new spider naevi may be indicative of a deterioration in liver function and regression may occur with improved function.⁴ Indeed the patient in case report 2 had a number of prominent facial spider naevi, which regressed rapidly after transplantation.

Pulmonary arteriovenous abnormalities in liver disease were first shown in the 1960s. Postmortem examinations of patients with cirrhosis and severe hypoxaemia clearly showed anatomical arteriovenous connections,¹ which occur in association with poor liver function. This combination leads to a very poor prognosis.¹³

With the advent of transplantation it became important to discover if severe hypoxaemia improved after liver transplant. If it did not it would have to be seen as a comparative contraindication as the chronic and sometimes severe hypoxia would undoubtedly impair graft survival. In the early 1980s a number of reports suggested that hypoxia was irreversible such as a patient who finally died within three months of his third transplant with severe hypoxia.⁵ Recent studies, however, measuring pulmonary vascular resistance and using nuclear medicine techniques to calculate arteriovenous shunting have shown that pulmonary arteriovenous malformations do close after liver transplantation⁶ and with improved general treatment, including good immunosuppression, the restoration of normal liver function is associated with resolution of hypoxia. A more recent report of reversal of intrapulmonary shunts after transplantation was associated with reversal of digital clubbing.⁷ This finding is in accordance with a case report in 1968⁸ of two siblings with cirrhosis of unknown aetiology who both developed intrapulmonary shunts, cyanosis, and digital clubbing. In one child liver function returned to normal over three years with resolution of the shunts and clubbing, whereas the younger

Figure 3: Arterial phase of digital subtraction angiography, showing a large feeding artery and filling of the arteriovenous malformation.

sibling deteriorated and died of severe liver failure and hypoxaemia.

Profound changes in general circulatory dynamics are common in both acute liver failure and advanced chronic liver disease.² The severity of these changes is related to the degree of liver dysfunction⁹ and therefore might be expected to reverse after liver transplantation. The most prominent change in the general circulation is the development of a high cardiac output state with a low systemic vascular resistance, hypotension, and decreased cardiovascular responsiveness.² Close monitoring of patients undergoing liver transplantation¹⁰ shows that the high cardiac output and low systemic vascular resistance before operation revert to normal by 64 hours after the transplant with no significant change in the systemic blood pressure. Since then more recent studies have shown a persistence of high cardiac output, and high azygous blood flow *v* controls¹¹ though there is a significant decrease in all of these values compared with before transplant.¹² Persistently high hepatic blood flow is also seen and is possibly related to graft denervation. Neither of these studies could control for drugs required after the transplant.

The structural changes, such as the arteriovenous malformations we describe and the previously reported pulmonary arteriovenous malformations and clubbing reverse only slowly after liver transplant. Changes in systemic vascular resistance and cardiac output may also take some months to resolve and they may never completely return to normal when compared with controls. In our case the arteriovenous malformation had clinically halved in size by three weeks after transplant but further significant resolution occurred over nine months. It is thought that the cardiovascular changes discussed above result from high circulating concentrations of catecholamines, gastrointestinal peptides,¹³ prostaglandins,¹⁴ and oestrogens causing generalised vasodilatation. We postulate that the high concentrations of these substances also act on latent arteriovenous shunts in the systemic circulation as well as in the lungs. Once formed it may take some time for arteriovenous shunts to close after the original stimuli have been

removed, this finding is in keeping with findings related to the other cardiovascular and pulmonary vascular changes discussed here.

In conclusion, this is the first report of systemic arteriovenous malformations in association with advanced liver disease although pulmonary arteriovenous abnormalities have been recognised for over 30 years.¹ In both of the cases reported the arteriovenous malformations increased in size as the liver function deteriorated and in the patient who had a liver transplant, the resumption of normal liver function was associated with reduction in size of the arteriovenous malformation.

- Berthelot P, Walker JG, Sherlock S, Reid L. Arterial changes in the lung in cirrhosis of the liver-lung spider naevi. *N Engl J Med* 1966; 274: 291-8.
- Lunzer MR, Manghani KK, Newman SP, Sherlock SPV, Bernard AG, Ginsberg J. Impaired cardiovascular responsiveness in liver disease. *Lancet* 1975; ii: 382-5.
- Krowka MJ, Cortese DA, Dickson ER, Jacksonville FL, Rochester MN. Hepatopulmonary syndrome: clinical course in 57 patients. [Abstract]. *Hepatology* 1992; 16: 83.
- Sherlock S. *Disease of the liver and biliary system*. 8th Ed. Oxford: Blackwell Scientific, 1989.
- Sang Oh K, Bender TM, Bowen A, Ledesma-Medina J. Plain radiographic, nuclear medicine and angiographic observations of hepatogenic pulmonary angiodysplasia. *Pediatr Radio* 1983; 13: 111-5.
- Eriksson LS, Soderman C, Ericzon B-G, Eleborg L, Wahren J, Hedenstierna G. Normalization of ventilation/perfusion relationships after liver transplantation in patients with decompensated cirrhosis: evidence for a hepatopulmonary syndrome. *Hepatology* 1990; 12: 1350-7.
- Stoller JK, Moodie D, Schiavone WA, Vogt D, Broughan T, Winkelman E, *et al*. Reduction of intrapulmonary shunt and resolution of digital clubbing associated with primary biliary cirrhosis after liver transplantation. *Hepatology* 1990; 11: 54-8.
- Silverman A, Cooper MD, Moller JH, Good RA. Syndrome of cyanosis, digital clubbing, and hepatic disease in siblings. *J Pediatr* 1968; 72: 70-80.
- Brailion A, Cales P, Valla D, Gaudy D, Geoffroy P, Lebrec D. Influence of the degree of liver failure on systemic and splanchnic haemodynamics and on response to propranolol in patients with cirrhosis. *Gut* 1986; 27: 1204-9.
- Glauser FL. Systemic haemodynamic and cardiac function changes in patients undergoing orthotopic liver transplantation. *Chest* 1990; 98: 1210-5.
- Hadengue A, Lebrec D, Moreau R, Sogni P, Durand F, Gauden C, *et al*. Persistence of systemic and splanchnic hyperkinetic circulation in liver transplant patients. *Hepatology* 1993; 17: 175-8.
- Navasa M, Feu F, Garcia-Pagan JC, Jimenez W, Llach J, Rimola A, *et al*. Haemodynamic and humoral changes after liver transplantation in patients with cirrhosis. *Hepatology* 1993; 17: 355-60.
- Henriksen JH, Staun-Olsen P, Fahrenkrug P, Ring-Larsen H. Vasoactive intestinal polypeptide (VIP) in cirrhosis: arteriovenous extraction in different vascular beds. *Scand J Gastroenterol* 1980; 15: 787-92.
- Bruix J, Bosch J, Kravetz D, Masta IR, Rodés J. Effects of prostaglandin inhibition on systemic and hepatic haemodynamics in patients with cirrhosis of the liver. *Gastroenterology* 1985; 88: 430-5.